REMARKS:

In the February 12, 2007 Non-final Office Action, the examiner rejected claims 1-13. Applicants respectfully request that the Examiner reconsider the rejection of claims 1-13 in light of the remarks herein.

Rejection under 35 U.S.C. §112, First and Second Paragraphs:

The Examiner has rejected claims 1-3, 6, 9, and 12-13 under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. The Examiner has also rejected claims 1-13 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner has rejected claims 1-3, 6, 9, and 12-13 with respect to "bioactive agent" having insufficient description to show that the inventors had possession of compositions comprising the entire genus. Furthermore, with respect to "liquid polymer," claims 1-13 were rejected under §112, second paragraph as being "confusing." The Examiner stated that the term "liquid polymer… can be interpreted as 'polymer in solution' which is ionically bonded or a 'polymer which is liquid'."

With respect to the Examiner's rejection of claims 1-3, 6, 9, and 12-13 under 35 U.S.C. §112, first paragraph, Applicants respectfully traverse. The invention as recited in Claim 1 is directed to a liquid ionic conjugate. The claimed conjugate comprises an absorbable liquid polymer and a bioactive agent, wherein said conjugate is formed through at least partial ionic binding between said bioactive agent and said absorbable liquid polymer. The application describes that the liquid conjugate may be made by contacting the basic aspects or moieties of said bioactive agent (or said polymer as the case may be) with the acidic aspects or moieties of said liquid polymers (or said bioactive agent as the case may be) "under conditions effective to cause sufficient proton transfer whereby ionic conjugation… occurs." (See page 4, lines 1-6.)

Applicants submit that in assessing the written description requirement, the Examiner has focused on the number of examples provided in the application rather than the real inquiry, which is whether Applicants have adequately described their invention in the specification to convey to the public the subject matter which is being claimed (See MPEP, Section 2163, page 2100-165). Note that "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met . . . even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis,* 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). Applicants submit that the aforementioned principle also applies in the instant situation. The specification describes "bioactive agent" in a way sufficient to convey to the public what Applicants

are claiming. As discussed above, the specification is clear in indicating that the bioactive agent is involved in an ionic conjugation with the absorbable liquid polymer. It is true that there are multitudes of bioactive agents, but their chemical structures are well known in the art. Those of ordinary skill in the art are well familiar with, once knowing the molecular structure of any bioactive agent, being able to identify whether it is capable of ionic conjugation. "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." See *Hybritech Inc. V. Monoclonal Antibodies*, Inc., 231 USPQ 81, 94 (Fed. Cir.1986). Additionally, as discussed, the subject specification provides description of those qualities which would render a bioactive agent of being capable of ionic conjugation. For example, the specification indicates that basic, e.g. amine groups, or acidic, e.g. carboxyl groups, can provide suitable ionic attraction to generate ionic bonding whereby the conjugates of the invention form (see page 3, lines 3-6; and page 4, lines 31-34). Hence, Applicants maintain that the subject application provides adequate written description of the genus "bioactive agents" for purposes of its relevance to the claimed invention.

As regards to the Examiner's rejection of claims 1-13 under 35 U.S.C. §112, second paragraph, Applicants respectfully traverse. The Examiner stated that "the word 'liquid polymer' in claims 1 and 13 is confusing [because] it can be interpreted as 'polymer in solution' which is ionically bonded or a 'polymer which is liquid." Applicants respectfully submit that the term "liquid polymer" is not "confusing" as it is specifically defined in the application and possesses a meaning well known to one skilled in the art.

The specification specifically defines liquid polymers of the present invention as being functionalized i.e. as bearing moieties that provide suitable ionic attraction with the aforesaid bioactive agents to generate the ionic bonding whereby the ionic conjugates of the present invention form. The specification further describes the polymers of the invention as having certain characteristics such as being absorbable and <u>being in the liquid state</u> (page 3, lines 34-35). Other non-limiting characteristics of "liquid polymer" that is the subject of the present invention are also clearly defined and described in the specification. (See page 3, lines 23-37). Furthermore, one skilled in the art would understand the term "liquid polymer" to refer to a one-component liquid that is solvent free, whereas the term "polymer in solution" means a polymer in a solvent. Thus, Applicants respectfully submit that the term "liquid polymer" is not confusing but rather clearly defined and described in the specification and its meaning is well understood to a person having ordinary skill in the art.

Applicants respectfully request that the Examiner reconsider and withdraw the rejection of Claims 1-3, 6, 9, and 12-13 under 35 U.S.C §112, first paragraph, and Claims 1-13 under 35 U.S.C §112, second paragraph.

<u>Rejection under 35 U.S.C. §102(b)</u>:

The Examiner has rejected claims 1-8 and 13 under 35 U.S.C. §102(b) as being anticipated by Shalaby et al. U.S. Patent Number 5,714,159. Applicants respectfully note that the Examiner incorrectly cited Shalaby et al. as U.S. 5,714,<u>519</u>. The correct patent number is U.S. 5,714,<u>159</u>. According to the

Examiner, the present invention is anticipated by Shalaby et al. to U.S. 5,714,159. The Examiner stated that "Shalaby discloses a hydrogel-forming, self-solvating, absorbable polyester copolymers capable of selective, segmental association into a compliant hydrogel mass on contact with an aqueous environment." The Examiner further stated that the "liquid composition made of component A [as detailed in Shalaby et al.] with or without drug or bioactive agent can form hydrogels upon contacting a liquid environment," (Referencing column 12, lines 10-12 Shalaby et al.), and that "the liquid conjugate, 'Component A' in this case can combine with bioactive drugs such as calcium hence proving the ionic bond linkage between the liquid conjugate and the bioactive drug."

Applicants respectfully traverse. Applicants request that the Examiner reconsider and withdraw this rejection of claims 1-8 and 13 under 35 U.S.C §102(b) because Shalaby does not disclose each and every element of the claimed invention of the subject application. The present invention of the subject application claims a liquid conjugate comprising a bioactive agent and an absorbable liquid polymer being at least partially ionically bonded together. Shalaby in U.S. 5,714,159 does not disclose a liquid ionic conjugate. Shalaby et al. discloses a copolymer comprising a base component designated "Component A." The Applicants respectfully submit that the Examiner has mischaracterized and misunderstood "Component A" as a "liquid conjugate" when, for instance, the Examiner stated: "The liquid conjugate, "Component A" in this case can combine with bioactive drugs such as calcium (column 12, lines 58-59) hence proving the ionic bond linkage between the liquid conjugate and the bioactive drug" (Office Action page 6, last sentence of §102(b) rejection). "Component A" is not a liquid conjugate. Instead, component A is a single-component copolymer, block polymer "compris[ing] a molecular chain having a hydrophilic block… and a relatively hydrophobic polyester block… [further comprising] a molecular structure having" a well defined formula (column 7, lines 3-19).

Furthermore, the Applicants respectfully disagree with the Examiner's conclusion that column 12, lines 58-59 is evidence "proving the ionic bond linkage between the liquid conjugate (i.e. "component A" to use the Examiner's misnomer) and the bioactive drug [such as calcium]." Column 12, lines 58-59 does not disclose an ionic bond linkage but rather only discloses a use of the "copolymer formulations [of the Shalaby invention in U.S. 5,714,159] for prolonged, controlled dispensing… drugs and agents, such as, for example… ions, such as calcium…" The use of the copolymer formulation of the Shalaby invention mentioned in column 12, lines 58-59 does not provide any suggestion nor discloses an ionic bond linkage between the copolymer Component A and a biologically active agent, and thus, does not disclose a liquid conjugate.

Instead, column 12, lines 55-59 actually discloses an example of the formation of a hydrogel (a process known as gelation, or as described in the Shalaby reference, "the copolymer formulations") by addition of Ca^{2+}-ions. In this regard, Applicants submit in the Supplemental Information Disclosure Statement herewith pages 22-23 of the publication entitled Polymer chemistry and hydrogel systems, published in the Journal of Physics: Conference Series 3 (2004) by E.H. Schacht (hereafter "Schacht").

Schacht teaches that the process of gelation may be caused by several mechanisms including by the addition of calcium (See pages 22-23, Figure 2). Thus, column 12, lines 58-59 discloses one example of the "copolymer formulation" of the Shalaby reference by addition of calcium ions which causes gelation via ionic interactions between the copolymer and the calcium ions, and not between the copolymer and a biologically active agent. Therefore, the addition of calcium causes gelation and does not form a liquid conjugate comprising an absorbable liquid polymer and a biological agent being at least partially ionically bonded together.

The Applicants respectfully note another instance where the Examiner has reached an unsupported conclusion when the Examiner stated: "The copolymer described by Shalaby is capable of being injected into living tissues (column 6, line 57) (hence proving that the copolymer is [a] liquid conjugate)" (Office Action page 5, last sentence middle paragraph). Column 6, line 57 mentions an object of the Shalaby invention which "provide[s] such a copolymer for constituting or constructing a carrier of vaccines, living cells, or viable tissue for sustaining biological functions both in vitro and in vivo." Column 6, line 57 does not refer to a copolymer "capable of being injected into living tissues," as the Examiner asserts, and even if it did, a copolymer capable of being injected into living tissues does not support the conclusion that the copolymer is a liquid conjugate. A copolymer that is capable of being injected into living tissues does not necessarily have to be a conjugated-polymer, and may be in a solid, semi-solid, or liquid state, or, as disclosed and claimed in the Shalaby reference in U.S. 5,714,159, undergo "selective, segmental association into a compliant hydrogel mass on contact with an aqueous environment" (column 19, lines 31-34). Thus, contrary to the Examiner's assertion, a copolymer "capable of being injected into living tissues" does not necessarily "prov[e] that the copolymer is [a] liquid conjugate."

In order for the Shalaby reference to anticipate the present invention of the subject application, it must meet each and every element of the claimed invention. The inquiry is "whether the subject of the barring activity met [each and every element] of the claim, and thus was an embodiment of the claimed invention." *Dana Corp. v. Am. Axle & Mfg., Inc.*, 279 F.3d 1372, 1375-76, 61 U.S.P.Q.2d 1609, 1611 (Fed. Cir. 2002), quoting *Scaltech Inc. v. Retec/Tetra, L.L.C.*, 178 F.3d 1378, 1383, 51 U.S.P.Q.2d 1055, 1058 (Fed. Cir. 1999). *See also*, *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1319 (Fed. Cir.), *reh'g denied*, 2004 U.S. App. LEXIS 4125 (2004). The Shalaby reference to U.S. 5,714,159 does not disclose a liquid conjugate and it does not disclose an ionic conjugate, and it therefore fails in at least two aspects to anticipate the claimed invention which is directed to a liquid conjugate comprising an absorbable liquid polymer and a bioactive agent being at least partially ionically bonded together.

As the Examiner noted, Shalaby et al. discloses a copolymer, block polymer designated "component A" comprising a molecular chain having a hydrophilic block and a relatively hydrophobic polyester block arranged in a molecular structure having a well defined formula (column 7, lines 3-19). This disclosure does not read on claim 1 of the present invention of the subject application which claims "a liquid conjugate." (Subject Application page 15, line 1). It is true that the Shalaby reference describes

"component A" as comprising "an inherent viscosity at 25 degrees C in chloroform ranging between 0.03 to 0.80 dl/g and can be present as a liquid at room temperature…" (column 10, lines 10-17). But this copolymer that is in the liquid state alone is not enough to read on claim 1 of the claimed invention of the subject application because it is not a conjugate comprising a bioactive agent.

Furthermore, a key feature of component A is its ability to "under[go] selective-segmental segregation to form a flexible, compliant, reversible gel which adheres to the surrounding tissues and acquires the configuration of the site." (column 10, lines 7-10). This microphase transformation may be done "with or without a biologically active agent" (column 10, lines 5-6), and if said transformation occurs with said biologically active agent, the agent "can be deposited, wholly or in part, on a solid carrier, designated 'Component B'… [where] Component B preferably is an absorbable, powder prior to mixing with Component A and, more preferably, Component B is an absorbable, microporous low molecular weight polyester which is highly crystalline and practically insoluble in Component A" (column 10, lines 55-61). Thus, the mixture of Component A and biologically active agent preferably involves an additional component that is "powder… highly crystalline" Component B, which suggests that said mixture is in part in the solid, semi-solid state. (See column 7, lines 30-38; and also Example II, lines 24-26 and 39-41). This mixture is not "a liquid conjugate" as claimed in the present invention of the subject application.

The Shalaby reference U.S. 5,714,159 fails to disclose "a liquid conjugate" as claimed in the subject application, and therefore, also fails to disclose a liquid conjugate comprising a bioactive agent at least partially ionically bonded to an absorbable liquid polymer. Claim 1 of the present invention of the subject application recites an element of the liquid conjugate having "said bioactive agent and said absorbable liquid polymer being at least partly ionically bonded together to form said liquid conjugate." (Subject Application page 15, line 1). This element is not disclosed in the Shalaby reference to U.S. 5,714,159. It is true that the Shalaby reference states that "Component A optionally comprises carboxylic end-groups formed by any known technique in the art, such as, for example, end-group succinylation" (column 7, lines 19-23). In addition, "[this] facilitates ionically binding a biologically active agent or drug [further comprising] an absorbable carrier," to Component A (column 7, lines 30-33). However, the ionic characteristic of Component A is optional and moreover is not indicated to result in a liquid ionic conjugate. In fact, the ionic characteristic of component A should be minimized to avoid adversely affecting the essential properties of component A to undergo "selective, segmental association into a compliant hydrogel mass on contact with an aqueous environment" (column 19, lines 31-34). This microphase transformation is an essential element, function, or feature of component A of the Shalaby reference.

In this regards, Applicants submit in the Supplemental Information Disclosure Statement herewith pages 107-149 of the publication entitled Hydrogels for Pharmaceutical and Biomedical Applications, published in Critical Reviews in Therapeutic Drug Carrier Systems by Kashyap et al. (hereafter "Kashyap"). Kashyap teaches that "the swelling characteristics of hydrogels [i.e. component A] are

important in characterization for biomedical applications" and that the "ionic character affects the hydrophilic and swelling properties of the hydrogel," where said ionic character in turn "affects the pH sensitivity of the gel" (See pages 111-112). "The presence of pendent acidic or basic groups that either accept or release protons in response to changes in pH makes a polymer pH sensitive. These polyelectrolytes have a large number of ionizable groups that display a big difference in swelling…" (see page 117). Thus, optional end-group carboxylation of component A via succinic anhydride may "render component A more receptive to basic drugs," but one having ordinary skill in the art would understand that this step is not preferred since it may defeat the principal purpose of Component A which is to undergo "selective, segmental association into a compliant hydrogel mass on contact with an aqueous environment" (See column 10, lines 2-5; and See also column 19, lines 31-34).

For the reasons explained above, Applicants contend that the Shalaby reference to U.S. 5,714,159 does not anticipate each and every element of the claimed invention of the subject application. Thus, the Applicants respectfully request that the Examiner withdraw the §102(b) rejection.

Rejection under 35 U.S.C. §103(a)

The Examiner has rejected claims 1-3, 6, 4-10, and 12-13 under 35 U.S.C. §103(a) as being unpatentable over Shalaby (U.S. Patent No. 5,714,159) in view of Kim et al. (U.S. Patent No. 6,232,304). The Examiner, in making this rejection, noted that Shalaby et al. discloses copolymers which undergo microphase transformation upon contacting an aqueous environment. The Examiner further stated that Shalaby discloses that said copolymer "optionally comprises a bioactive agent," and that, even though Shalaby did not specifically teach the bioactive agent such as ziprasidone (aryl-heterocyclic compound), Kim et al. discloses "aryl-heterocyclic drug such as ziprasidone." The Examiner concludes that "since the object of both Shalaby and Kim et al. is to increase the drug solubility, it would have been obvious to one of ordinary skilled in the art… to utilize ziprasidone in the liquid conjugate as a bioactive drug or alternately to use polymers and carboxyl-bearing polymers or carboxyl-bearing block/segment as forwarded by Shalaby, with ziprasidone to make liquid conjugate…"

The Applicants respectfully disagree and traverse. Applicants respectfully request that the Examiner withdraw this rejection in light of the following remarks. It is true that Kim et al. describes the solubilization of ziprasidone, which is a "bioactive drug." But Kim et al. does not specify the use of the ionic conjugation approach nor direct the attention of one ordinarily skilled in the art to a polymer as described in the present application. Kim et al. describes the combination of a cyclodextrin and ziprasidone in order to improve the solubility of ziprasidone. Cyclodextrin is not a polymer. Moreover, contrary to the Examiner's assertion, the object of the Shalaby reference and the Kim reference is not the same. The object of the Shalaby reference is directed towards "providing a protective barrier to prevent post-surgical adhesion, treatment of defects in conduits such as blood vessels, and controlled release of a biologically active agent…" (column 1, lines 16-19). This is contrary to the object of the Kim reference

which is directed to improving the solubility of ziprasidone. This is just one reason why a person of ordinary skill in the art would not even combine the Shalaby reference and the Kim reference as the Examiner has proposed.

With respect to the Kim reference and unlike the liquid polymers described in the present application, a cyclodextrin is not a polymer. In this regard, Applicants submit in the Supplemental Information Disclosure Statement herewith pages 165-168 of the Handbook of Pharmaceutical Excipients, Third Edition, edited by Arthur H. Kibbe (hereinafter "Kibbe"). Kibbe teaches that cyclodextrins are "crystalline, nonhygroscopic, cyclic oligosaccharides derived from starch" (see the second column of Page 165). Moreover, looking at the structure provided in Column 1 of Page 165 to show examples of cyclodextrins, one can see that none of the examples of cyclodextrins are ionic. Furthermore, the cyclodextrins depicted in Column 1 comprise only seven units and have molecular weights ranging from 972 to 1297. Thus, a cyclodextrin is not polymeric. It may be considered oligomeric, but not polymeric.

Furthermore, Kim et al. also does not disclose any specific ionic conjugate, but "ionic" is another element of the invention as recited in the claims of the subject application. As explained in the preceding paragraph, Kibbe shows that cyclodextrins are not necessarily ionic in nature. Kibbe teaches that for cyclodextrins "the internal surface of the cavity is hydrophobic while the outside of the torus is hydrophilic" and that "this arrangement permits the cyclodextrin to accommodate a guest molecule within the cavity so forming an inclusion complex" (Column 2, Page 165, of Kibbe). Thus, the interaction between guest molecule and cyclodextrin is not indicated by Kibbe to be ionic, but rather hydrophobic. Referring to the examples of cyclodextrin-ziprasidone combinations provided in Table I (Column 9) of Kim et al. (to which the Examiner also referred), note that the combination of ziprasidone free base and HPBCD does not involve an ionic conjugation. Neither ziprasidone free base nor HPBCD are ionic molecules. Nonetheless, the combination of ziprasidone free base and HPBCD resulted in the increase in aqueous solubility from 0.3 μA/ml to 0.26 mgA/ml. True, a combination of ziprasidone and a cyclodextrin can increase the solubility of ziprasidone, and this is taught by Kim et al. But the means taught by Kim et al. for achieving increased solubility are not the same as the means described in the subject application. A person having ordinary skill in the art would not have been directed by Kim et al. to improve the solubility of ziprasidone using an absorbable liquid polymer to form a liquid ionic conjugate.

The Examiner further contends that because the object of both the Shalaby and the Kim references are the same, "it would have been obvious to one of ordinary skilled in the art… to utilize ziprasidone in the liquid conjugate…." The Examiner is mistaken in three respects: (1) Shalaby et al. is directed to "providing a protective barrier to prevent post-surgical adhesion, treatment of defects in conduits such as blood vessels, and controlled release of a biologically active agent…" (column 1, lines 16-19), while Kim et al. is not; (2) as described above, the Shalaby reference does not disclose a liquid conjugate but rather discloses a copolymer, block polymer designated "component A" comprising a molecular chain having a hydrophilic block and a relatively hydrophobic polyester block arranged in a molecular structure having a

well defined formula (column 7, lines 3-19); and (3) each reference, in fact, fails to disclose and suggest the combination of elements, functions, or features in the manner of the claimed invention of the subject application.

Contrary to the Examiner's assertion, the object of the Shalaby reference and the Kim reference are not the same. But even if a person of ordinary skill in the art were nonetheless to combine these references, neither reference, when read alone or when read together, suggests the combination of the claimed invention. When each reference is read alone, each reference is missing an element, function, or feature of the claimed invention. In the case of the Kim reference, a disclosure of an ionic conjugate and an absorbable liquid polymer is missing even though ziprasidone is disclosed. In the case of the Shalaby reference, a disclosure of a liquid conjugate comprising a biologically active agent such as ziprasidone is missing even though a distinct copolymer which may be liquid and which may optionally comprise ionizable end groups is disclosed. When the references are read in view of the other, it is important to acknowledge that neither reference discloses or suggests a liquid conjugate comprising an absorbable liquid polymer and a bioactive agent being at least partially ionically bonded together.

For the reasons explained above, Applicants contend that Kim et al. and Shalaby et al. do not direct one ordinarily skilled in the art to the use of the ionic conjugation polymer approach described in the subject application.

The Examiner also cited the Robins et al. reference as interest.

Robins et al. (U.S. Patent Number 7,119,246) was filed in 2005 well after the filing date of the present application. Additionally, it deals with "solutions of a neutral polymer" and not a carboxyl-bearing, solvent-free liquid as taught by the subject application.

a polyester formed by grafting a glycolide, lactide, .epsilon.-caprolactone, p-dioxanone, trimethylene carbonate or combinations thereof, onto the hydroxylic or amino-end groups of a hydrophilic polymer precursor i.e., Y. Hydrophilic block Y preferably comprises a polyoxyethylene, poly(oxyethylene-b-oxypropylene), polypeptide, polyalkylene oxamate, a polysaccharide, or derivatives thereof, or a liquid, high molecular weight polyether glycol interlinked with oxalate or succinate functionalities in linear or branched form.

In a preferred embodiment, Component A comprises a polyethylene glycol having a molecular weight of about 400 Daltons which is pre-interlinked with succinate or oxalate bridges to increase the length of the hydrophilic block and, thus, the molecular weight of A without favoring its crystallization. That is, the hydrophilic prepolymer "Y" having hydroxylic end-groups, is end-grafted with a mixture 60/40 dl-lactide/glycolide to produce a block copolymer having a hydrophilic block fraction "Y" of about 0.25. To render Component A more receptive to basic drugs, its end-groups can optionally be carboxylated, for instance,

by their acylation with succinic anhydride. Component A, with or without a biologically active agent, is introduced to a biological target site using conventional means and, thereafter, undergoes selective-segmental segregation to form a flexible, compliant, reversible gel which adheres to the surrounding tissues and acquires the configuration of the site. Component A of the invention more preferably comprises an inherent viscosity at 25.degree. C. in chloroform ranging between 0.03 to 0.80 dL/g and can be present as a liquid at room temperature, or practically amorphous material (with less than 5% crystallinity) with a T.sub.g of less than 25.degree. C., which can be extruded through a die or administered through a syringe needle.

Conclusion

Based on the above remarks, Applicants submit that the claimed invention is patentable over the references cited by the Examiner and provided with the Supplemental Information Disclosure Statement herewith. Applicants earnestly solicit the earliest possible notification of allowable subject matter.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, the Examiner is kindly invited to telephone Applicants' undersigned attorney at the number provided.

Respectfully submitted,

Date: July 11, 2007

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